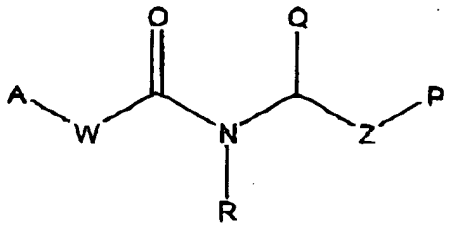
Allowed 8-16-2002

APPENDIX A

1. A compound of Formula I,



(I)

wherein
A is a MetAP-2 inhibitory core;
W is O or NR;
each R is, independently, hydrogen or alkyl;
Z is –C(O)- or -alkylene-C(O)-;
P is NHR, OR or a peptide consisting of one to about one hundred amino acid residues connected at the N-terminus to Z;
Q is a linear, branched or cyclic alkyl or aryl;
or
Z is –alkylene-O- or –alkylene-N(R)-;
P is hydrogen or a peptide consisting of from one to about one hundred amino acid residues connected to Z at the carboxyl terminus;
Q is a linear, branched or cyclic alkyl or aryl;
and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 wherein Z is –C(O)- or C_1-C_4-alkylene-C(O)-.

3. The compound of Claim 2 wherein Z is -C(O)- or C_1-C_2-alkylene-C(O)-.

4. The compound of Claim 2 wherein Q is linear, branched or cyclic C_1-C_6-alkyl, phenyl or naphthyl.

5. The compound of Claim 4 wherein Q is isopropyl, phenyl or cyclohexyl.

6. The compound of Claim 1 wherein Z is C_1-C_6-alkylene-O- or C_1-C_6-alkylene-NR-.

7. The compound of Claim 6 wherein Z is C_1-C_4-alkylene-O- or C_1-C_4-alkylene-NH-.

8. The compound of Claim 7 wherein Z is C_1-C_2-alkylene-O- or C_1-C_2-alkylene-NH.

9. The compound of Claim 6 wherein Q is linear, branched or cyclic C_1-C_6-alkyl , phenyl or naphthyl.

10. The compound of Claim 9 wherein Q is isopropyl, phenyl or cyclohexyl.

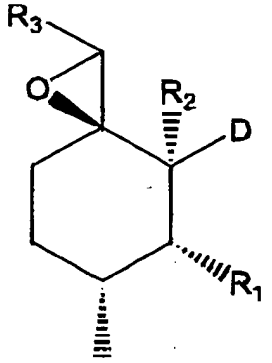
11. The compound of Claim 1 wherein each R is, independently, hydrogen or linear, branched or cyclic C_1-C_6-alkyl.

12. The compound of Claim 11 wherein each R is, independently, hydrogen or linear or branched C_1-C_4-alkyl.

13. The compound of Claim 12 wherein each R is, independently, hydrogen or methyl.

14. The compound of Claim 13 wherein each R is hydrogen.

15. The compound of Claim 1 wherein A is of Formula II,



(II)

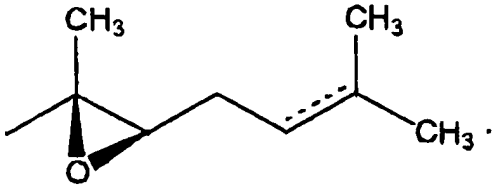
wherein

R_1 is hydrogen or alkoxy;

R_2 is hydrogen or hydroxy;

R_3 is hydrogen or alkyl; and

D is linear, branched or cyclic alkyl or arylalkyl; or D is of the structure



16. The compound of Claim 15 wherein R_1 is C_1-C_4-alkoxy.

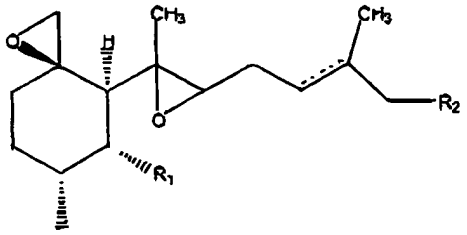
17. The compound of Claim 16 wherein R_1 is methoxy.

18. The compound of Claim 15 wherein R_3 is hydrogen or C_1-C_4-alkyl.

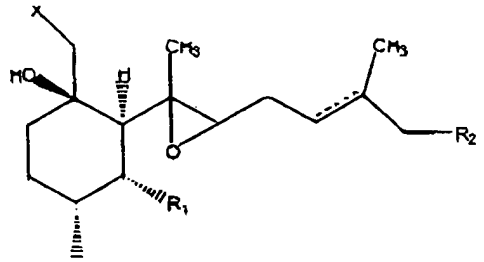
19. The compound of Claim 18 wherein R_3 is methyl.

20. The compound of Claim 15 wherein D is linear, branched or cyclic C_1-C_6-alkyl; or aryl-C_1-C_4-alkyl.

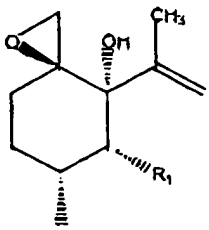
21. The compound of Claim 1 wherein A is selected from the group consisting of



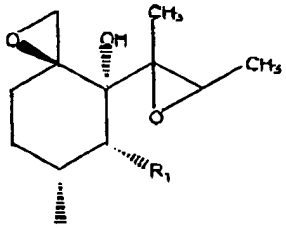
(IV)



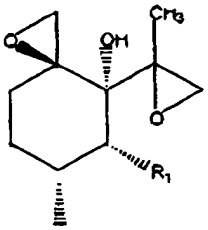
(V)



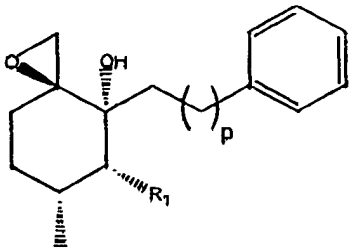
(VI)



(VII)



(VIII)



(IX)

Wherein

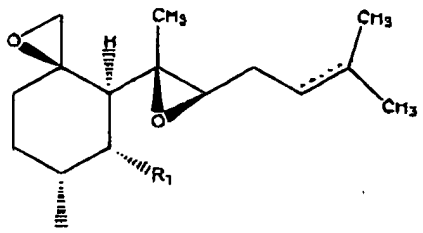
p is an integer from 0 to 10;

R_1 is hydrogen, -OH or C_1-C_4-alkoxy;

X is a leaving group; and

R_2 is H, OH, amino, C_1-C_4-alkylamino or di(C_1-C_4-alkyl)amino.

22. The compound of Claim 21 wherein A is of the formula



23. The compound of Claim 1 wherein P comprises from 1 to about 20 amino acid residues.

24. The compound of Claim 23 wherein P comprises an amino acid sequence which is a substrate for a matrix metalloprotease.

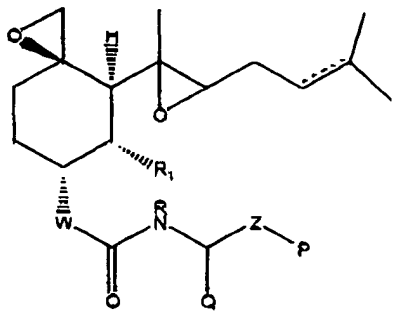
25. The compound of Claim 24 wherein the matrix metalloprotease is selected from the group consisting of MMP-2, MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and MMP-26.

26. The compound of Claim 25 wherein the matrix metalloprotease is MMP-2 or MMP-9.

27. The compound of Claim 26 wherein P comprises the sequence -Pro-Leu-Gly-Xaa-, wherein Xaa is a naturally occurring amino acid residue.

28. The compound of Claim 27 wherein P comprises the sequence Pro-Cha-Ala-Abu-Cys(Me)-His-Ala (SEQ ID NO:16).

29. A compound of the formula



wherein
W is O or NR;
each R is, independently hydrogen or a C_1-C_4-alkyl;
Q is a linear, branched or cyclic C_1-C_6-alkyl; or aryl;
R_1 is hydroxy, C_1-C_4-alkoxy or halogen;
Z is –C(O)- or C_1-C_4-alkylene-C(O)-;
P is NHR, OR, or a peptide comprising 1 to 100 amino acid residues attached to Z at the N-terminus; or
Z is alkylene-O or alkylene-NR; and
P is hydrogen or peptide comprising 1 to 100 amino acid residues attached to Z at the C-terminus;
or a pharmaceutically acceptable salt thereof.

30. The compound of Claim 29 wherein
W is O or NH;
Z is alkylene-O or alkylene-NH;
Q is isopropyl;
R_1 is methoxy; and
P comprises from 1 to 15 amino acid residues.

31. The compound of Claim 30 wherein
W is O; and
P comprises 10 or fewer amino acid residues.

32. The compound of Claim 29 wherein P comprises from 1 to about 20 amino acid residues.

33. The compound of Claim 32 wherein P comprises an amino acid sequence which is a substrate for a matrix metalloprotease.

34. The compound of Claim 33 wherein the matrix metalloprotease is selected from the group consisting of MMP-2, MMP-1, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13 and MMP-26.

35. The compound of Claim 34 wherein the matrix metalloprotease is MMP-2 or MMP-9.

36. The compound of Claim 35 wherein P comprises the sequence -Pro-Leu-Gly-Xaa-, wherein Xaa is a naturally occurring amino acid residue.

37. The compound of Claim 36 wherein P comprises the sequence Pro-Cha-Ala-Abu-Cys(Me)-His-Ala (SEQ ID NO:16).

38. An angiogenesis inhibitor compound selected from the group consisting of

{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-butyric acid methyl ester;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-butyric acid methyl ester;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-4-methyl-pentanoic acid methyl ester;

{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-phenyl-acetic acid methyl ester;

(1-Carbamoyl-2-methyl-propyl)-carbamic acid-(3*R*, 4*S*, 5*S*, 6*R*)-5-methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

(1-Carbamoyl-2-methyl-propyl)-carbamic acid-(3*R*, 4*S*, 5*S*, 6*R*)-5-methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

(1-Hydroxymethyl-2-methyl-propyl)-carbamic acid-(3*R*, 4*S*, 5*S*, 6*R*)-5-methoxy-4-[(2*R*, 3*R*)- 2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3,3-dimethyl-butyric acid methyl ester;

Cyclohexyl-2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-acetic acid methyl ester;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-pentanoic acid methyl ester;

[1-(1-Carbamoyl-2-hydroxy-ethylcarbamoyl)-2-methyl-propyl]-carbamic acid-(3*R*, 4*S*, 5*S*, 6*R*)-5-methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

2-(3-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl}-ureido)-3-methyl-butyramide;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-butyric acid;

~~N-Carbamoyl-GlyArgGlyAspSerPro-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

N-Carbamoyl- GlyArgGlyAspTyr(OMe)~~Arg~~ Glu-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-butyl)-~~oxiranyl~~]-1-oxa-spiro[2.5]oct-6-yl ester;

N-Carbamoyl-GlyArgGlyAsp-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-~~methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

N-Carbamoyl-GlyArg{3-amino-(3-pyridyl)}-proprionic acid-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

~~N-Carbamoyl-GlyProLeuGlyMetTrpAlaGly-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

N-Carbamoyl-GlyProLeuSar-OH-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

~~N-Carbamoyl-GlyProLeuGly-OH-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

~~Ac-ProLeuGly-MetTrpAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*)~~ 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-

~~but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl butanol) ester~~;

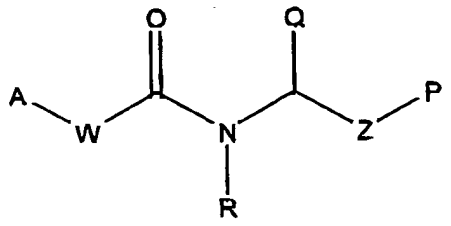
Ac-ProLeuGlyMetGly-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester;

H-MetTrpAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester; and

H-MetGly-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester; ~~and~~ .

~~Ac-ProLeuGlyMetAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester.~~

39. A method of treating an angiogenic disease in a subject, comprising administering to the subject a therapeutically effective amount of an angiogenesis inhibitor compound comprising the structure



(I)

wherein

A is a MetAP-2 inhibitory core;

W is O or NR;

each R is, independently, hydrogen or alkyl;

Z is –C(O)- or -alkylene-C(O)-;

P is NHR, OR or a peptide consisting of one to about one hundred amino acid residues connected at the N-terminus to Z;

Q is hydrogen, linear, branched or cyclic alkyl or aryl, provided that when P is –OR, Q is not hydrogen;

or

Z is –alkylene-O- or –alkylene-N(R)-;

P is hydrogen or a peptide consisting of from one to about one hundred amino acid residues connected to Z at the carboxyl terminus;

Q is hydrogen, linear, branched or cyclic alkyl or aryl, provided that when P is hydrogen, Q is not hydrogen; and a pharmaceutically acceptable salt thereof,
thereby treating the angiogenic disease in the subject.

40. The method of claim 39, wherein said angiogenic disease is an autoimmune disease.

41. The method of claim 40, wherein said autoimmune disease is rheumatoid arthritis.

42. The method of claim 39, wherein said angiogenic disease is cancer.

43. The method of claim 39, wherein said subject is a human.

44. The method of claim 39, wherein said angiogenesis inhibitor compound is administered to said subject using a pharmaceutically acceptable formulation.

45. The method of claim 39, wherein the angiogenesis inhibitor compound is administered to the subject intravenously.

46. The method of claim 39, wherein the angiogenesis inhibitor compound is administered to the subject intramuscularly.

47. The method of claim 39, wherein the angiogenesis inhibitor compound is administered to the subject orally.

48. The method of claim 39, wherein the angiogenesis inhibitor compound is selected from the group consisting of

{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-butyric acid methyl ester;

2-{(3*R*, 4*S*, 5*S*, 6*R*)-5-Methoxy-4-[(2*R*, 3*R*)-2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonylamino}-3-methyl-butyric acid methyl ester;

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methyl-3-(3-methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

~~N-Carbamoyl-GlyArgGlyAsp-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-butyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

N-Carbamoyl-GlyArg{3-amino-(3-pyridyl)}-proprionic acid-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

~~N-Carbamoyl-GlyProLeuGlyMetTrpAlaGly-NH_2-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

N-Carbamoyl-GlyProLeuSar-OH-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;

~~N-Carbamoyl-GlyProLeuGly-OH-(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester;~~

Ac-ProLeuGly-MetTrpAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester;

~~Ac-ProLeuGlyMetGly-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester;~~

H-MetTrpAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester;

H-MetGly-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester; ~~and~~

~~Ac-ProLeuGlyMetAla-(2*R*-{(3*R*, 4*S*, 5*S*, 6*R*) 5-methoxy-4-[(2R,3R)2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yloxycarbonyl} amino-3-methyl-butanol) ester.~~

49. The compound of claim 29, wherein

W is O;

each R is, independently hydrogen;

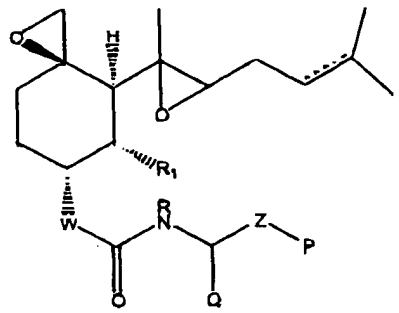
Q is a linear, branched or cyclic C_1-C_6-alkyl; or aryl;

R_1 is C_1-alkoxy;

Z is –C(O);

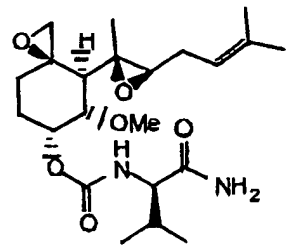
P is NHR.

50. A compound of the formula



wherein
W is O;
each R is, independently hydrogen;
Q is a linear, branched or cyclic C_1-C_6-alkyl; or aryl;
R_1 is C_1-alkoxy;
Z is –C(O);
P is NHR;
or a pharmaceutically acceptable salt thereof.

51. An angiogenesis inhibitor compound comprising the structure



or a pharmaceutically acceptable salt thereof.

52
~~51.~~ An angiogenesis inhibitor compound comprising the structure (1-Carbamoyl-2-methyl-propyl)-carbamic acid-(3*R*, 4*S*, 5*S*, 6*R*)-5-methoxy-4-[(2*R*, 3*R*) -2-methyl-3-(3-methyl-but-2-enyl)-oxiranyl]-1-oxa-spiro[2.5]oct-6-yl ester, or a pharmaceutically acceptable salt thereof.